1.3.1 SUMMARY PRODUCT CHARACTERISTICS (SmPC)

<table>
<tr><td>1</td><td>Name of the Finished Medicinal Product:</td></tr>
<tr><td>1.1</td><td>Product Name:
Bupivacaine Hydrochloride Injection BP</td></tr>
<tr><td>1.2</td><td>Strength : 5 mg/ml</td></tr>
<tr><td>1.3</td><td>Pharmaceutical Form: Injection</td></tr>
<tr><td>2</td><td>Qualitative and Quantitative Compositions:</td></tr>
<tr><td></td><td>Qualitative Declaration:
Active component
INN Name: Bupivacaine Hydrochloride
Quantitative Declaration:
Each ml contains
Bupivacaine Hydrochloride BP
Eq. to Anhydrous Bupivacaine Hydrochloride…....5.0 mg.
Methyl Paraben BP……..0.8 mg.
(As Preservative)
Propyl Paraben BP……...0.2 mg.
(As Preservative)
Water for Injection BP…….q.s.

<table>
<tr><th>Sr. No.</th><th>Content Name</th><th>Quality Standard</th><th>Quantity/ml</th></tr>
<tr><td>1</td><td>Bupivacaine Hydrochloride equivalent to anhydrous Bupivacaine Hydrochloride</td><td>BP</td><td>5.1 mg*</td></tr>
<tr><td>2</td><td>Methyl Paraben</td><td>BP</td><td>0.8mg</td></tr>
<tr><td>3</td><td>Propyl Paraben</td><td>BP</td><td>0.2mg</td></tr>
<tr><td>4</td><td>Sodium Chloride</td><td>BP</td><td>8.0mg</td></tr>
<tr><td>5</td><td>Sodium Hydroxide</td><td>BP</td><td>q.s.#</td></tr>
<tr><td>6</td><td>Hydrochloric Acid</td><td>BP</td><td>q.s.#</td></tr>
<tr><td>7</td><td>Water for Injection</td><td>BP</td><td>q.s to 1.0 ml</td></tr>
</table>

* 2% overages added
# For pH adjustment only.
BP: British Pharmacopoeia.</td></tr>
<tr><td>3</td><td>Pharmaceutical form: Injection
Description: A colourless or almost colourless solution</td></tr>
<tr><td>4</td><td>Clinical Particulars:</td></tr>
<tr><td>4.1</td><td>Therapeutic Indications:</td></tr>
</table>

Bupivacaine Hydrochloride Injection BP is indicated for the production of local anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures.

The routes of administration and indicated Bupivacaine Hydrochloride Injection BP concentrations are:

Local infiltration	0.25%
Peripheral nerve block	0.25% and 0.5%
Sympathetic block	0.25%

IT IS NOT RECOMMENDED FOR INTRAVENOUS REGIONAL ANESTHESIA.

4.2 Posology and method of administration

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered.

For specific techniques and procedures, refer to standard textbooks.

In recommended doses, Bupivacaine produces complete sensory block, but the effect on motor function differs with different concentrations.

Bupivacaine Hydrochloride Injection — provides motor blockade, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

The duration of anesthesia with Bupicaine is such that for most indications, a single dose is sufficient.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of Bupivacaine up to 175 mg without epinephrine; more or less drug may be used depending on individualization of each case.

These doses may be repeated up to once every three hours.

Recommended Concentrations and Doses of Bupivacaine Hydrochloride Injection BP

Type of Block	**Conc.**	**Each Dose**		**Motor Block[1]**
		(mL)	**(mg)**	
Local infiltration	**0.25%**	**up to max.**	**up to max.**	**-**
Peripheral nerves	**0.5%**	**5 to max.**	**25 to max.**	**moderate to complete**
	0.25%[4]	**5 to max.**	**12.5 to max.**	**moderate to complete**
Sympathetic	**0.25%**	**20-50**	**50-125**	**-**

[1]With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intraabdominal surgery.

Method of Administration: Local infiltration & Nerve block.

4.3	**Contra-indications:** Bupivacaine Hydrochloride Injection BP is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death. Bupivacaine Hydrochloride Injection BP is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of Bupivacaine solutions.
4.4	**Special warning and precautions for use:** **WARNINGS** Local anesthetics should only be employed by clinicians who are well versed in diagnosis and management of dose-related toxicity and other acute emergencies which might arise from the block to be employed, and then only after insuring the immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies. **PRECAUTIONS** It is not for Spinal anesthesia. **General:** The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies.
4.5	**Interaction with other drugs, other forms of interactions:** Bupivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. certain anti-arrhythmics, such as lidocaine, since the systemic toxic effects are additive. Specific interaction studies with Bupivacaine and anti-arrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution should be advised.
4.6	**Usage in pregnancy& Lactation** **Pregnancy:** **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. Bupivacaine Hydrochloride Injection BP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. **Lactation:** Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from Bupivacaine, a decision should be made whether to discontinue nursing or not administer Bupivacaine, taking into account the importance of the drug to the mother.
4.7	**Effects on ability to drive and operate machine:** Depending on the dose and method of administration, Bupivacaine can have a transient effect on movement and coordination.
4.8	**Undesirable effects:** Reactions to Bupivacaine Hydrochloride Injection BP are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation. The most commonly encountered acute adverse experiences which demand immediate counter-measures are related to the central nervous system and the cardiovascular system. **Central Nervous System Reactions:** These are characterized by excitation and/or

	depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered. **Cardiovascular System Reactions:** High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. **Allergic:** Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology (including severe hypotension). **Neurologic:** Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid. Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.
4.9	**Overdose and special antidotes :** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution. **Management of Local Anesthetic Emergencies:** The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered. The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred. If necessary, use drugs to control the convulsions. Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.
5	**Pharmacological Properties:**
5.1	Pharmacodynamic Properties: **Pharmacotherapeutic Group (ATC Code) : N01B B01** Local anesthetics block the generation and the conduction of nerve impulses, presumably

	by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone. Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.
5.2	**Pharmacokinetic Properties:** The onset of action with Bupivacaine is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with Bupivacaine than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced. Local anesthetics appear to cross the placenta by passive diffusion. Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized. After injection of Bupivacaine for peripheral nerve block in man, peak levels of Bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. The half-life of Bupivacaine in adults is 2.7 hours and in neonates 8.1 hours. In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients. Amide-type local anesthetics such as Bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecoloxylidine is the major metabolite of Bupivacaine. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of Bupivacaine is excreted unchanged in the urine. When administered in recommended doses and concentrations, Bupivacaine does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.
5.3	**Preclinical Safety Data :** Bupivacaine hydrochloride is a well established active ingredient.

6	**Pharmaceuticals Particulars:**
6.1	**List of Excipients:** Methyl Paraben BP Propyl Paraben BP Sodium Chloride BP Sodium Hydroxide BP Hydrochloric Acid BP Water for Injection BP
6.2	**Incompatibilities:** In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
6.3	**Shelf life:** 24 Months
6.4	**Special precautions for storage:** Store below 30°C. Protect from light.
6.5	**Nature and contents of container:** Bupivacaine Hydrochloride Injection BP 5mg/ml is packed in 20 ml clear glass vial USP Type - I with bromo butyl rubber plug and red colour aluminium flip off seal. 1 such vial packed in a carton along with pack insert.
6.6	**Special precaution for disposal :** Not Applicable
7	**Registrant:** **Marketing Authorization Holder:** **M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD.** Address : Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway Lagos Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : --- **Manufacturing Site Address:** **M/s THEMIS MEDICARE LIMITED** Sector 6A, Plot No. 16, 17 & 18, IIE, SIDCUL, Haridwar – 249 403, Uttarakhand, INDIA. Telephone: 91-1334-239321/22 Fax: 91-334-239217 E-mail: hwdgmtech@themismedicare.com
8	**Date of Revision of the Text:** Not Applicable
9	**Dosimetry (if applicable):** Not Applicable
10	**Instruction for preparations of Radiopharmaceutical (if applicable):** Not Applicable